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Study on the construction of nomogram prediction model for prognostic assessment of heart failure patients based on serological markers and echocardiography

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Abstract. – OBJECTIVE: We aimed to construct a nomogram prediction model for prognostic assessment of patients with heart failure (HF) based on serological markers and echocardiography.

PATIENTS AND METHODS: A total of 200 HF patients admitted to the Second Affiliated Hospital of Nanchang University from January 2018 to January 2020 were selected as the research objects. According to the New York Heart Association (NYHA) cardiac function classification, they were divided into 3 groups, including 65 cases of grade II, 97 cases of grade III, and 38 cases of grade IV. Three groups of echocardiographic parameters were compared [including left ventricular ejection fraction (LVEF), left ventricular end-diastolic diameter (LVEDD), left ventricular end-systolic diameter (LVESD), left ventricular end-systolic volume (LVESV)], differences in serum markers brain natriuretic peptide (BNP), soluble growth-stimulating expression gene 2 (sST2) and the Modified Early Warning Score (MEWS). The patients were divided into two groups according to their clinical outcomes during the follow-up period, including 52 cases in the death group and 148 cases in the survival group. The clinical data of the two groups were compared, and multi-factor logistic regression analysis was performed to screen out the independent risk factors affecting the patient's death. A nomogram model of the patient's mortality risk was constructed based on the independent risk factors. Receiver operating characteristic (ROC) curves and calibration curves were used to evaluate the discrimination and accuracy of the nomogram model.

RESULTS: As the cardiac function class of elderly chronic heart failure (CHF) patients increases, LVEDD, LVESD, sST2, and MEWS increase and LVEF decreases ($p<0.05$). Multifactor analysis results showed that LVEF, LVEDD, sST2, and MEWS were independent factors affecting the clinical outcome of patients. The AUCs predicted using LVEF, LVEDD, sST2, and MEWS alone were 0.738, 0.775, 0.717, 0.831, and 0.768, respectively. There is a certain degree of discrimination, and the model has extremely high accuracy.

CONCLUSIONS: MEWS, LVEDD, and sST2 increase as the NYHA cardiac function grade of HF patients increases and LVEF decreases, which can reflect the severity of the disease to a certain extent. Additionally, the nomogram model established based on this has a high predictive value for the long-term prognosis of patients and can formulate effective intervention measures for quantitative values.

Key Words:
Heart failure, Echocardiography, Serum markers, Long-term prognosis, Cardiac function class.

Introduction

Heart failure (HF) is a variety of heart structural or functional diseases that lead to impaired ventricular filling or ejection function, and cardiac output cannot meet the metabolic needs of body tissues. It is a comprehensive disease characterized by congestion of the pulmonary circulation and/or systemic circulation, and insufficient blood perfusion of organs and tissues. The main symptoms of the disease are difficulty breathing, fluid retention, and limited physical activity. This is due to the structure of the heart and/or insufficient cardiac output and/or abnormal function during exercise, leading to increased intracardiac pressure and/or resting[1]. In Western countries, heart failure has reached epidemic proportions, with extremely high morbidity and mortality, and its prevalence is increasing[2]. Therefore, developing valuable HF diagnosis, treatment, and prognosis plans is a key part of the latest acute and chronic HF guidelines.

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Although the age-adjusted incidence of HF may be declining, the overall incidence of cardiovascular disease is increasing as a result of the aging population, possibly reflecting better management of cardiovascular disease[3]. Currently, the incidence of HF in Europe is approximately 3/1,000 persons/year (all age groups) or 5/1,000 persons/year in adults[4]. The prevalence of HF in adults appears to be 1-2%[3]. Because studies typically include only identified/diagnosed HF cases, the true prevalence is likely higher[5]. The prevalence increases with age, from about 1% of people under 55 years of age to more than 10% of people 70 years of age or older[6].

Cardiovascular disease has always been one of the leading causes of death in China. Accounting for more than 40% of deaths, mortality and morbidity have been on the rise in recent years[7]. Previous studies have suggested that neuroendocrine, inflammation, oxidative stress, myocardial remodeling and other factors are potential mechanisms leading to the pathogenesis of HF[8]. Among these factors, inflammation is considered to be a major contributor, according to Briasoulis et al[9]. Inflammation can lead to cardiovascular damage. Pro-inflammatory mediators play a great role in the occurrence and development of HF[10]. HF is not a single pathological diagnosis, but a complex clinical syndrome involving multiple pathophysiological pathways, so patients' symptoms need to be distinguished[11]. In addition to myocardial injury, systemic inflammation or distant organ failure [eg, chronic kidney disease (CKD), altered collagen homeostasis, or pulmonary hypertension (PH)] also plays an important role[11]. Therefore, diagnostic and therapeutic interventions need to address a wide variety of conditions and cannot be limited to a single aspect.

According to the 2021 China Heart Failure Quality Control Report, heart failure is the terminal stage of various cardiovascular diseases. The incidence and mortality of heart failure are increasing year by year, and it has become a serious public health problem in our country. Currently, heart failure is diagnosed and graded based on clinical symptoms, combined with ejection fraction (EF), NT-proBNP, and cardiac structural or functional abnormalities. Many previous studies[12-14] have shown that assessing left ventricular systolic function through left ventricular volume and EF is a powerful method to predict the long-term prognosis of various heart diseases. In recent years, with the development of medical technology and equipment, various new technology layers for detecting cardiac function have been gradually discovered. Many studies[15,16] at home and abroad have shown that imaging manifestations and serological indicators are of great value in etiological diagnosis, risk classification, and prognosis guidance of heart failure.

In recent years, many studies[17] have found that various serological indicators are closely related to the prognosis of patients with heart failure. Therefore, paying close attention to the serological indicators of patients with heart failure, accurately assessing the cardiac function of patients with heart failure, and comprehensively assessing the risk of patients with heart failure are crucial to reducing mortality and improving quality of life. Many studies[18] have found that inflammation and oxidative stress are closely related to the occurrence of cardiovascular diseases; among them, neutrophils (N) are related to inflammatory response, while lymphocytes (L) are related to stress response. Therefore, the Neutrophil-to-Lymphocyte Ratio (NLR) can reflect the different degrees of balance between inflammation and oxidative stress[19]. Among them, NLR is considered to be a predictor of reduced cardiac function in patients with heart failure, and it also has important predictive value for the prognosis of patients with heart failure[20,21]. Currently, it was found that serum markers of thyroid hormone[22], serum BNP15, serum sST2[23] and so on are related to the prognosis of HF patients. In addition, one of the effective diagnostic methods for HF is echocardiography. In addition to producing two-dimensional images of the cardiovascular system, echocardiography uses continuous ultrasound waves or pulses to measure the velocity of blood and heart muscle tissue at any location precisely. This allows detection of heart valve area function, abnormal left and right heart connections, valve regurgitation, and calculation of cardiac output. It is safe, effective, reproducible, and easy to operate. Echocardiography can detect changes in the anatomical structure of the heart in real-time, reflecting the degree of remodeling and functional changes.

This study collected the clinical data of 200 HF patients admitted to our hospital from January 2018 to January 2020. Analyzed serum markers and echocardiographic parameters to explore the value of disease severity and long-term prognosis of HF patients and provided references for effective clinical prevention and treatment in the future.

Patients and Materials

Basic Information

A total of 200 HF patients admitted to The Second Affiliated Hospital of Nanchang University from January 2018 to January 2020 were selected as the research objects in this retrospective study. All patients use standard, normative, and commonly used clinical examination methods, which do not involve the collection and preservation of human biological samples. This study was approved by the ethics committee of The Second Affiliated Hospital of Nanchang University (No. 2020-023). The research protocol complies with the medical research ethics principles of the Declaration of Helsinki. HF patients were followed up for 3 years through outpatient visits, readmissions, telephone calls, etc. The clinical outcomes of the patients during the follow-up period were recorded and divided into the survival and death groups.

Inclusion and Exclusion Criteria

Inclusion criteria: (1) Age >18 years old and <85 years old; (2) HF meets the relevant standards of the "Chinese Heart Failure Diagnosis and Treatment Guidelines 2018", and all included heart failure patients have left ventricular ejection fraction ≤50%; (3) according to the New York Heart Association (NYHA) cardiac function classification, the cardiac function of the heart failure group was divided into Level II: Heart disease patients with mildly limited physical activity and no conscious symptoms at rest, but may experience heart failure symptoms such as fatigue, palpitations, dyspnea, and decreased activity tolerance during normal activities; Level III: patients with heart disease whose physical activities are significantly limited. Less than usual activities can cause obvious fatigue, dyspnea, decreased activity tolerance, edema of both lower limbs, carotid artery distension and other clinical symptoms and signs of heart failure. Level IV: patients with heart disease cannot engage in any physical activity. They may also experience heart failure symptoms such as fatigue, difficulty breathing, and decreased activity tolerance when resting quietly. The above symptoms will be aggravated after slight activity; (4) no history of percutaneous coronary intervention or other major surgical procedures in the last 3 months.

Patients will be excluded from the study if they meet any of the following conditions: (1) coexisting heart valve disease or congenital heart disease; (2) severe liver and kidney insufficiency, severe infection, or undergoing hemodialysis; (3) presence of chronic obstructive pulmonary disease or any other condition that may impact cardiac function; (4) blood system diseases or blood loss anemia; (5) thyroid diseases or autoimmune diseases; (6) malignant tumors or acute cerebrovascular diseases; (7) pregnant or lactating women.

Methods

Clinical data such as age, gender, smoking, drinking, diabetes, hypertension, coronary heart disease, etc. of patients were collected. 5 mL of venous blood was extracted from the patient on an empty stomach in the early morning, centrifuged at 3,000 r/min, and the serum was stored at low temperature. The enzyme-linked immunosorbent assay was used to determine the serum soluble growth-stimulating expression gene 2 (sST2) level; the electrochemical luminescence immunoassay was used to determine the serum brain natriuretic peptide (BNP) level. An ultra-sounding map was created using VIVID-7 color ultrasound instruments with a probe frequency range of 1 to 5 MHz. This helped determine various measurements, including the patient's left ventricular ejection fraction (LVEF), left ventricular end-diastolic diameter (LVEDD), left ventricular end-systolic diameter (LVESD), and left ventricular end-systolic volume (LVESV).

Observation Indicators

We utilized the Modified Early Warning Score (MEWS) for assessing the severity of CHF patients, examining five indicators: systolic blood pressure, heart rate, respiration, body temperature, and level of consciousness. Each indicator ranges from 0 to 3 points, with a minimum of 0 points and a maximum of 14 points. The sum of the five indicators is MEWS. The higher the MEWS, the more serious the patient's condition. MEWS standards are shown in Table I.

Statistical Analysis

The data in this research were analyzed using statistical product and service solution (SPSS) 26.0 software (IBM Corp., Armonk, NY, USA), including counting data and measurement data. The former is represented by [n (%)] and the Chi-square is used for testing, while the latter is represented by Mean ± Standard Deviation, and the *t*-test is used for testing. If $p<0.05$, it can be confirmed that there is a significance in the data difference. Factors with statistically significant differences in the univariate logistic analysis were included in the multi-factor logistic analysis, and independent risk factors were used to construct a nomogram model of patient mortality risk. The diagnostic value of each

Table I. MEWS scoring criteria.

Project	0 points	1 point	2 points	3 points
Systolic blood pressure (mmHg)	101-199	81-100	≥200 or 71-80	≤70
Heart rate (times/min)	51-100	41-50 or 101-110	≤40 or 111-129	≥130
Respiration (times/min)	9-14	15-20	21-29 or <9	≥30
Body temperature (°C)	35.0	35.0-38.4	<35.0 or ≥38.5	
Consciousness	Clear consciousness	Respond to sound	Respond to pain	No reaction

1 mmHg=0.133 kPa

element was analyzed using the Receiver Operating Characteristic (ROC) curve and calibration curve. The area under the ROC curve (AUC) ≥0.70 indicates that the model has better discrimination.

Results

Comparison of Echocardiographic Parameters, Serum Markers, and MEWS Scores in Patients with Different Cardiac Function Grades

The flow diagram is shown in Figure 1. Echocardiographic parameters, serum markers, and MEWS results of patients with different cardiac function grades showed that in HF patients, LVEDD, LVESD, BNP, sST2 levels and MEWS increased with the increase of cardiac function grade (Figure 2), while LVEF decreased, the difference was statistically significant (p<0.05). There was no statistically significant difference in LVESV between patients with different cardiac function grades (p>0.05) (Table II).

Comparison of Clinical Data of Patients with Different Clinical Outcomes

The patients were followed up for 3 years and found that 52 of the 200 patients died, with a mortality rate of 26.00%. The LVEDD, LVESD, BNP, sST2, and MEWS in the death group were higher than those in the survival group (Figure 3), and the LVEF was lower than that in the survival group. The difference was statistically significant (p<0.05) (Table III).

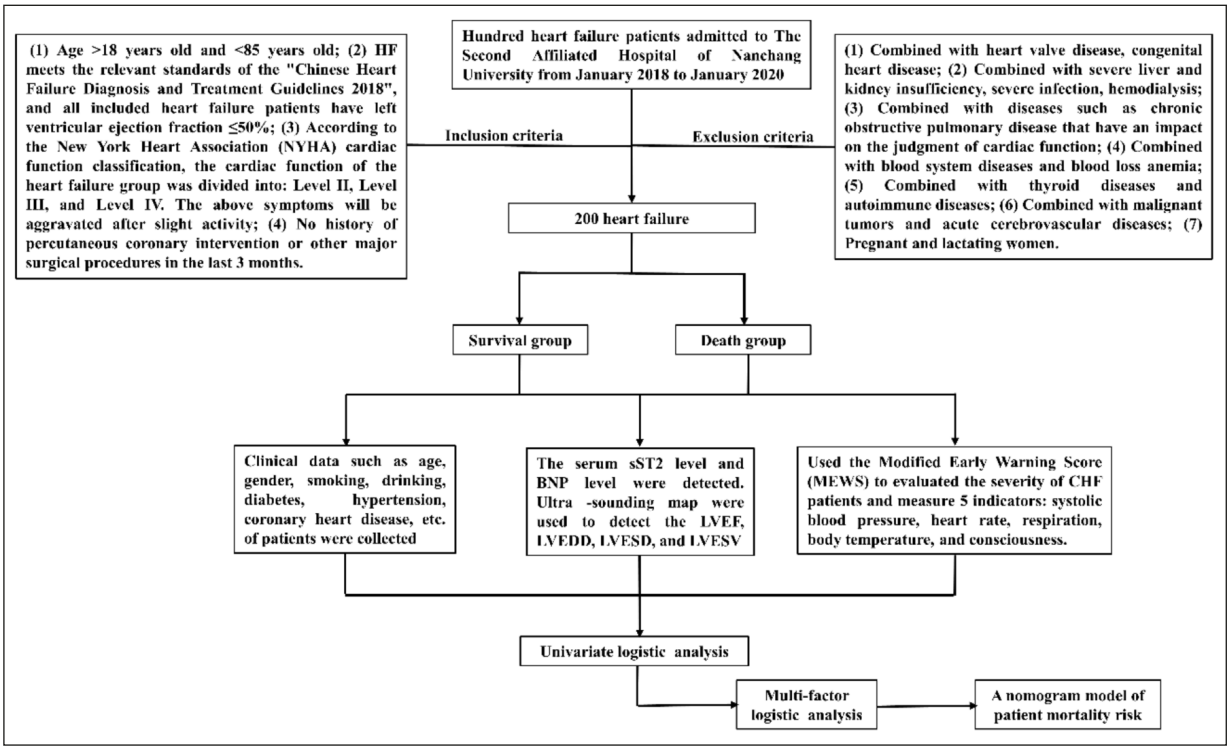

Figure 1. The flow diagram of this study.

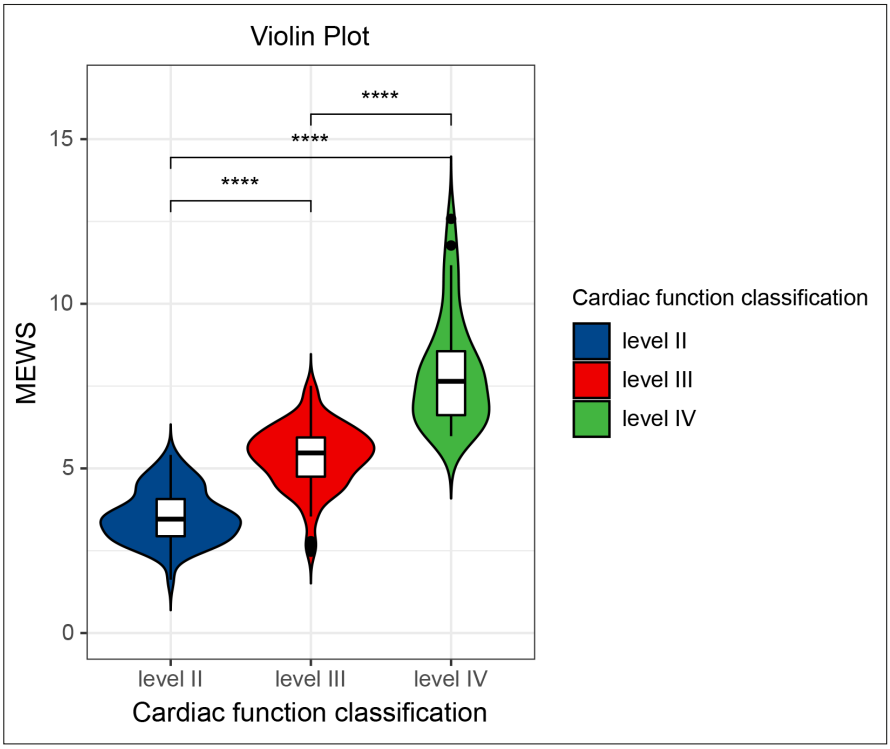

Figure 2. Violin plot comparing MEWS. ****p<0.0001.

Table II. Comparison of echocardiographic parameters, serum markers, and MEWS in patients with different cardiac function grades (Mean ± Standard Deviation).

Project	Cardiac function level II (n=65)	Cardiac function level III (n=97)	Cardiac function level IV (n=38)	*p*
LVEF (%)	45.47±7.59	34.59±8.05	27.54±5.95	0.000
LVEDD (mm)	50.21±7.54	59.38±8.21	63.57±6.05	0.000
LVESD (mm)	40.88±6.48	49.84±9.81	55.45±8.15	0.000
LVESV (mm)	89.48±9.50	91.25±11.59	92.05±9.58	0.729
BNP (pg/mL)	348.65±26.59	747.49±36.54	1,706.55±26.90	0.000
sST2 (ng/mL)	35.08±6.25	42.53±11.60	66.25±7.51	0.057
MEWS	3.55±0.79	5.35±0.95	7.91±1.68	0.000

Left ventricular ejection fraction (LVEF), left ventricular end-diastolic diameter (LVEDD), left ventricular end-systolic diameter (LVESD), brain natriuretic peptide (BNP), soluble growth-stimulating expression gene 2 (sST2), Modified Early Warning Score (MEWS).

Analysis of Influencing Factors of Death in HF Patients

The study considered the patient's mortality as the dependent variable and identified the statistically significant indicators as independent variables. The findings of the multi-factor logistic regression analysis revealed that LVEF, LVEDD, LVESD, sST2 levels, and MEWS were independent risk factors for patient death (Table IV).

A Nomogram Model for Predicting the Risk of Death in HF Patients

Based on the results of multivariate analysis, the nomogram prediction model for the death outcome of HF patients showed that as LVEDD, LVESD, sST2 levels and MEWS increase, LVEF decreases, and the corresponding score of the nomogram model increases, corresponding to the patient's increased risk of death (Figure 4).

Comparison of the Nomogram Model and the ROC Curve of Each Variable Predicting the Long-term Prognosis of Patients

In order to further evaluate the predictive value of LVEF, LVEDD, LVESD, sST2 levels, and MEWS on the long-term prognosis of patients, we used the ROC curve for analysis. The results showed that the AUCs predicted by LVEF, LVEDD,

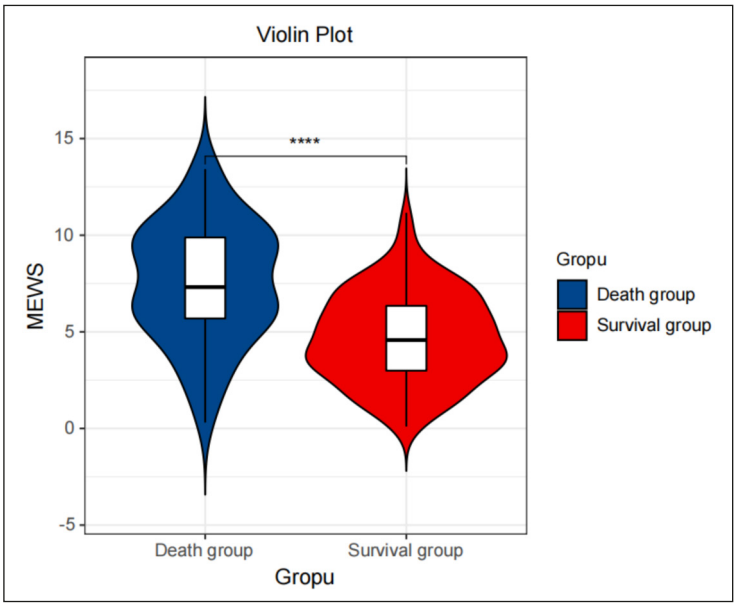

Figure 3. Violin plot comparing MEWS with different clinical outcomes. ****p<0.0001.

Table III. Comparison of clinical data for different clinical outcomes.

Project	Death group (n=52)	Survival group (n=148)	*p*
Age	68.75±10.55	61.26±9.56	0.000
Sex			
Male	28	86	0.593
Female	24	62	
Smoke	15 (28.85)	38 (25.68)	0.656
Drink alcohol	12 (23.08)	29 (19.59)	0.593
Diabetes	19 (36.54)	35 (23.65)	0.072
Hypertension	17 (32.69)	39 (26.35)	0.381
Coronary heart disease	21 (40.38)	38 (25.68)	0.045
Heart function classification			
Level II	8 (15.38)	48 (32.43)	
Level III	17 (32.69)	56 (37.84)	0.000
Level IV	27 (53.85)	44 (29.73)	
LVEF (%)	33.52±6.05	40.05±7.81	0.000
LVEDD (mm)	61.26±5.84	53.56±9.15	0.000
LVESD (mm)	50.26±7.05	44.15±8.55	0.000
LVESV (mm)	90.84±12.23	91.05±15.52	0.930
BNP (pg/mL)	1,545.20±26.55	542.40±37.59	0.000
sST2 (ng/mL)	54.15±8.59	42.05±9.55	0.000
MEWS	7.52±3.05	4.68±2.31	0.000

Left ventricular ejection fraction (LVEF), left ventricular end-diastolic diameter (LVEDD), left ventricular end-systolic diameter (LVESD), brain natriuretic peptide (BNP), soluble growth-stimulating expression gene 2 (sST2), Modified Early Warning Score (MEWS).

BNP, sST2, and MEWS alone were 0.738, 0.775, 0.717, 0.831, and 0.768, respectively, with a certain degree of discrimination (Table V, Figure 5).

Evaluation of Nomogram Models for Predicting Patient Mortality Risk

A calibration curve was drawn by combining the predicted value calculated by MEWS with LVEF, LVEDD, BNP, and SST2 and the observed value of the actual death risk. The results show that the discrimination ability of the prediction model is 0.959, indicating a high degree of accuracy (Figure 6).

Discussion

In this study, we constructed a nomogram prediction model for the prognostic assessment of HF

Table IV. Analysis of influencing factors of death in HF patients.

Factor	β	SE	Wald	*p*	OR	95% CI
LVEF	1.675	0.576	3.486	<0.001	1.140	1.080 - 1.202
LVEDD	1.516	0.334	2.252	<0.001	0.892	0.853 - 0.934
LVESD	0.964	0.847	2.145	<0.001	0.912	0.874 - 0.952
sST2	1.134	0.767	2.759	<0.001	0.863	0.823 - 0.905
MEWS	1.608	0.580	1.267	<0.001	0.661	0.571 - 0.764

Left ventricular ejection fraction (LVEF), left ventricular end-diastolic diameter (LVEDD), left ventricular end-systolic diameter (LVESD), soluble growth-stimulating expression gene 2 (sST2), Modified Early Warning Score (MEWS).

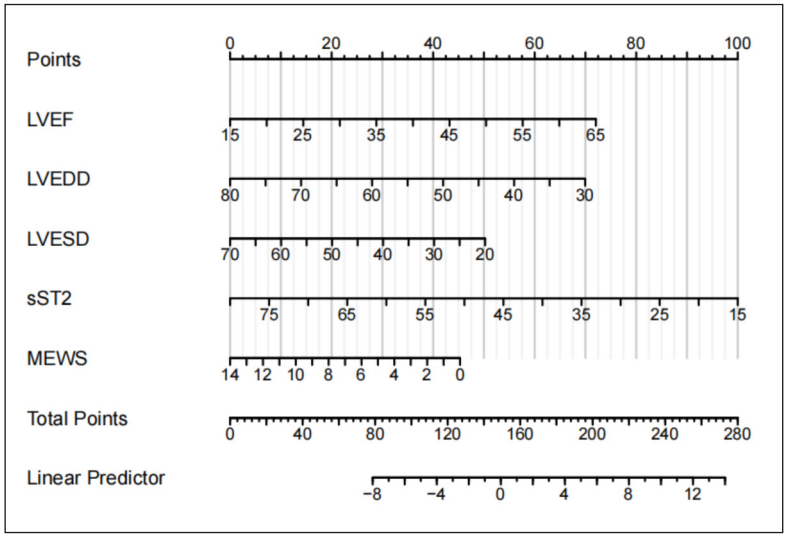

Figure 4. Nomogram prediction model of death risk in HF patients.

Table V. Nomogram prediction model and comparison of the predictive value of each variable.

Variable	AUC	Cut-off value	Sensitivity (%)	Specificity (%)	Positive predictive value (%)	Negative predictive value (%)
LVEF	0.738	40.67%	0.432	0.923	94.1	35.6
LVEDD	0.775	51.68 mm	0.473	0.981	98.6	45.4
LVESD	0.717	44.89 mm	0.554	0.846	91.1	40.0
sST2	0.831	51.735 ng/mL	0.845	0.712	89.3	55.6
MEWS	0.768	5.765 points	0.682	0.750	88.6	43.2

Left ventricular ejection fraction (LVEF), left ventricular end-diastolic diameter (LVEDD), left ventricular end-systolic diameter (LVESD), soluble growth-stimulating expression gene 2 (sST2), Modified Early Warning Score (MEWS).

patients based on serological markers and echocardiography. We found that the indexes of MEWS, LVEDD, and sST2 were increased as the NYHA cardiac function grade of HF patients increased, and LVEF was decreased, which can reflect the severity of the disease to a certain extent. The nomogram model established based on this had a high predictive value for the long-term prognosis of HF patients.

Heart failure is the final stage of various cardiovascular diseases and is vividly called "the final battlefield of cardiovascular diseases." It is a global disease that affects 26 million people worldwide and is one of the most serious public health problems in the world. Therefore, for HF patients, finding reliable indicators for assessing the severity of the disease and predicting long-term prognosis, closely monitoring high-risk patients, and focusing on intervention are the keys to reducing the mortality rate and improving the quality of life of patients[24]. At present, there are few markers for prognostic assessment, with low accuracy, poor sensitivity and specificity, and low predictive

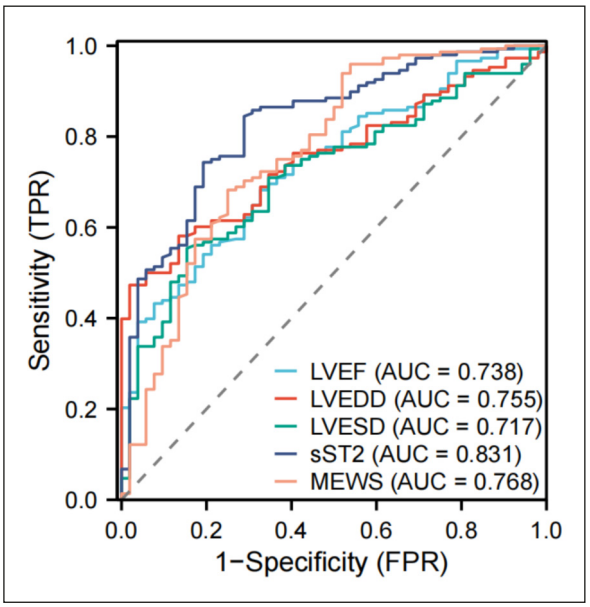

Figure 5. The ROC curve of each variable predicting the patient's prognosis.

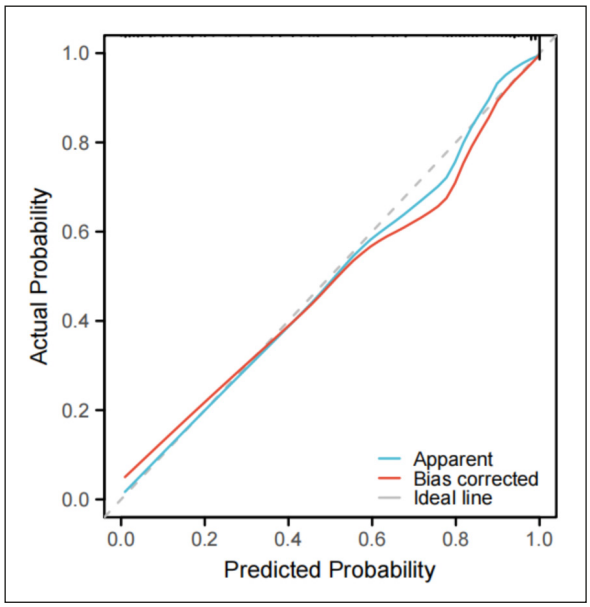

Figure 6. Calibration curve of a nomogram model predicting patient mortality risk.

value for prognosis. Therefore, it is urgent to find markers with long-term prognostic value.

MEWS comprehensively scores the patient's systolic blood pressure, heart rate, respiration, body temperature, and consciousness to quantify the patient's criticality. It can quickly predict the severity of a patient's condition and is not restricted by instruments, personnel, or locations. It is highly operable and is widely used in emergency departments and Intensive Care Units (ICUs)[14,25]. NYHA cardiac function classification not only can evaluate cardiac functions but is also an objective indicator for evaluating heart failure[26]. BNP is a polypeptide hormone that can reduce water and sodium retention and dilate blood vessels. According to Morishita et al[27], when the patient's ventricular load increases, BNP is stimulated to enter the blood, which can reflect ventricular pressure load and volume load. Usually, BNP is highly expressed in HF patients. Qin et al[28] have shown that BNP levels in HF patients are increased compared with healthy people. ST2 is an interleukin-1 receptor. The soluble subtype (sST2) and the transmembrane form (ST2L) are related to cardiovascular diseases. When myocardial cells are stretched, a large amount of sST2 is produced. Competitively inhibits the cardioprotective signaling pathway of interleukin (IL)-33/ST2L, leading to ventricular dysfunction. Serum sST2 level is a biomarker for evaluating the condition of heart failure and judging the prognosis of patients. Compared with other markers, the variation rate is lower[29]. Another study[30] found that serum sST2 levels in HF patients increased, and it was related to the severity of HF. Echocardiography is an objective, safe, and non-invasive examination technique for evaluating cardiac function and relevant parameters such as LVEF, LVEDD, and LVESD, and it can reflect left ventricular systolic and diastolic functions[31]. Studies[32] have shown that LVEF is negatively correlated with cardiac function classification, and LVEDD and LVESD are positively correlated with cardiac function classification. In addition, echocardiography can objectively evaluate the cardiac function classification of CHF patients[33]. Compared with the healthy group, LVEDD increased, and LVEF decreased in HF patients.

This study compared echocardiographic parameters, serum markers, and MEWS in patients with different heart function classes and found that with the increase of heart function class, LVEDD, LVESD, sST2 levels, and MEWS increased and LVEF decreased. It is suggested that LVEF, LVEDD, LVESD, sST2 levels, and MEWS can reflect the degree of cardiac dysfunction in HF patients. The results of this study show that LVEF, LVEDD, sST2, and MEWS are independent risk factors affecting patient death. The nomogram model constructed based on this connects the relevant indicators and obtains the corresponding model score according to the value of each element, and

the total score of each element is the risk of death in HF patients, which can intuitively show the individual risk of disease, and is easy to be popularized and applied in the clinic. In order to further evaluate the clinical value of each element on the long-term prognosis of patients, the ROC curve was used for analysis. The results showed that the AUCs predicted by LVEF, LVEDD, sST2, and MEWS alone were 0.738, 0.775, 0.717, 0.831, and 0.768, with a certain degree of discrimination. The calibration curve of the prediction model shows that the predicted value and the actual value are highly consistent, and the accuracy is extremely high. It is suggested that the joint detection of the above indicators can be strengthened in clinical practice to improve the evaluation value of the long-term prognosis of HF patients[33].

Conclusions

In conclusion, as the NYHA cardiac function classification increases, MEWS, LVEDD, and sST2 increase, and LVEF decreases, which can reflect the severity of the HF patient's condition to a certain extent. The nomogram model established based on this has a high predictive value for the long-term prognosis of patients, and it is helpful to formulate effective intervention strategies and provide a theoretical basis for specific quantitative values. Since this study is a single-center study with a limited sample size, it has certain limitations, and further multi-center, large-sample size studies are needed to verify the conclusions.

Authors' Contributions

Wei Yang conceived the structure of the manuscript. Fan Yu, Zixu Wang, and Jiao Yu did the experiments and made the figures. Fajia Hu, Rongjie Zhang and Yong Yuan reviewed and edited the manuscript. All authors read and approved the final manuscript.

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None.

Availability of Data and Materials

The datasets used and/or analyzed during the current study are available from the corresponding author upon reasonable request.

Conflict of Interests

The authors declare that they have no competing interests.

Informed Consent

All patients signed the informed consent form.

Ethics Approval

This study was approved by the Ethics Committee of The Second Affiliated Hospital of Nanchang University (No. 2020-023). The research protocol complies with the medical research ethics principles of the Declaration of Helsinki.

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